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EXAMINER
PRIEBE, SCOTT DAVID

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1632	34

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/126,945	Applicant(s) LIBERMANN ET AL.	
	Examiner Scott Priebe	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *157-294* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *203-206,209,212-228,243-246,249,252-256 and 259* is/are allowed.

6)☒ Claim(s) *157,158,161,164,167,170-181,184,187,190,193-202,207,208,210,211,236,237,239,240,247,248,250,251,257,258,260,261 and 264-* is/are rejected.

7)☒ Claim(s) *159,160,162,163,165,166,168,169,183,186,189,192,230 and 232* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

DETAILED ACTION

The amendment filed 12/21/01 has been entered. All previously pending claims have now been cancelled. Claims 157-294 have been added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

There is no antecedent basis in the specification as originally filed for claims 159, 162, 165, 168, 182, 185, 188, 191, 229, and 231. These claims recite polynucleotides in terms of 95% identity with respect to either SEQ ID NO: 1 or in terms of the polypeptide they encode relative to SEQ ID NO: 2, *without* recitation of retention of an "essential property" of a PDEF polynucleotide or polypeptide, as described on page 11. The originally filed specification at pages 11-14 is the only place where percent identity is discussed. This discussion is made only in the context of "variants". The first paragraph of this section on variants clearly defines "variant" polynucleotides and polypeptides as "retaining essential properties" of PDEF polynucleotides and polypeptides. However, the new claims do not recite any "essential property" being retained. The subject matter of these new claims is supported explicitly only by original claim 1 (and only

for at least 95%). In order to provide antecedent basis for these claims, it is suggested that the subject matter of original claims 1, part (a) , and 11, part (a) be inserted into the specification either before or after the discussion (page 5, line 20, to page 6, line 18) of polynucleotides which hybridize to SEQ ID NO: 1.

As indicated below, new claims broadly reciting "at least 90% identity" in the absence of a recited "essential property" are not supported in the original disclosure, and accordingly are rejected under 35 USC 112, first paragraph for the introduction of new matter.

Claim Rejections - 35 USC § 112

Claims 157-158, 161, 164, 167, 170-181, 184, 187, 190, 193-202, 207-208, 210-211, 236-237, 239-240, 247-248, 250-251, 257-258, 260-261, 264-294 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 157-158, 161, 164, 167, 170-181, 184, 187, 190, 193-202 are broadly drawn to a polynucleotide "comprising a first nucleic acid at least 90% identical to a reference nucleic acid" or "a nucleic acid encoding a first amino acid sequence at least 90% identical to a reference amino acid sequence". The claims do *not* recite that the polynucleotides or the polypeptides they encode retain "essential properties" of PDEF polynucleotides or polypeptides. Applicant has not indicated or explained where the specification supports these new claims. The originally filed

disclosure describes the invention in terms of percent sequence identity in only two locations: at pages 11-17, discussing "variants"; and in original claims 1 and 11, where the minimum percent identity is "at least 95%". The originally filed disclosure at page 11, lines 8-11, states that "variant" polynucleotides and polypeptides must "retain essential properties" of the disclosed PDEF polynucleotide, SEQ ID NO: 1, or polypeptide, SEQ ID NO: 2. The ensuing discussion mentions a lower limit of 90% sequence identity to SEQ ID NO: 1 or 2. However, the lower limit of 90% identity is discussed only in the context of the defined "variants". Claims 157-158, 161, 164, 167, 170-181, 184, 187, 190, 193-202 are directed to subject matter far broader than this disclosure in that these claims do not further limit the polynucleotides to "variants", i.e. those that retain, or encode a polypeptide that retains, an "essential property" of a PDEF polynucleotide or polypeptide, respectively. Original claims 1 and 11 do not require the polynucleotides or polypeptides to retain an essential property. *However,* they require a minimum percent sequence identity of "at least 95%". As indicated above, the original specification did not provide antecedent basis for this embodiment recited in claims 1 and 11. Consequently, there is no clear support for broadening the claimed invention to include embodiments where the first nucleic acid or first amino acid sequence is: "at least 90% identical to"; and less than 95% identical to, SEQ ID NO: 1 or SEQ ID NO: 2, respectively, wherein the first nucleic acid or first amino acid sequence *do not* retain an "essential property" of a PDEF polynucleotide or polypeptide. Inclusion of such broader embodiments is new matter.

Claims 176, 196, 199, 207, 210, 236, 239, 247, 250, 260, 273, and 276 each recite "first nucleic acid is operably associated with a *heterologous sequence*". Claims 177, 197, 200, 208, 211, 237, 240, 248, 251, 261, 274, 277, and 280 (and its dependent claims) each recite the "heterologous sequence" can be "an enhancer, a Kozak sequence, an operator", among other recited sequences supported in the specification in the paragraph bridging pages 27-28. The amendment filed 12/21/01 does not indicate where the specification supports these limitations. It is Applicant's burden to supply such information. MPEP 714.02, 2163.06 (section I). While the specification fully supports the linkage between heterologous sequences in general to the first nucleic acid, the same cannot be said for an "operable linkage". The phrase "operable association" implies some functional association between the heterologous sequence and the first nucleic acid. The specification only describes certain specific classes of sequence associated with transcription and translation of the "first nucleic acid" being "operably linked to the "first nucleic acid". This is not sufficient to convey the concept of something as broad as "heterologous sequence", any more than it was sufficient to convey the concept "heterologous regulatory sequence" recited in now cancelled claim 46, for example. The "an enhancer, a Kozak sequence, an operator" elements recited in the claims were not included in the original specification with the other specific sequences recited in the claims, and are unsupported.

In addition, these limitations are taken out of context in the case of claims 173, 174, 176, 177, 247, 248, 250, and 251 when compared to the limitations of their base claims which are directed to first nucleic acids with a particular structural relationship to SEQ ID NO: 1. The

specification discloses that operable linkage of transcription and translation elements are for production of protein. The claims from which these depend are not directed to polynucleotides that encode proteins, only that have a recited physical relationship to SEQ ID NO: 1. Most of the first nucleic acids embraced by these claims would not encode polypeptides that are structurally or, especially, functionally related to PDEF. It only takes a deletion or insertion of one or two nucleotides to change the translation frame, and such insertion/deletion variations are fully embraced by the claims. The specification describes polynucleotides defined in terms of their structural relationship to SEQ ID NO as being used for hybridization While some first nucleic acids embraced by these claims would encode polypeptides would be structurally very similar to PDEF, most would not.

Claims 264-279 recite that the nucleic acid encoding specific amino acid residues of SEQ ID NO: 2, which are disclosed as being epitopes, are fused to a heterologous nucleotide sequence encoding a heterologous polypeptide. As written, the claims appear to be directed to disclosed embodiments where the polynucleotide encodes a fusion protein comprising the heterologous polypeptide and an epitope sequence from SEQ ID NO: 2. However, the claim does not recite such a relationship between the "nucleic acid" and the "nucleotide sequence", the polynucleotide need not encode any fusion protein; and consequently is not supported by the specification. This part of the rejection would be overcome by inserting --in frame-- after "fused" in line 1 of claim 264, or by amending claim 264 to recite that the polynucleotide encoded a fusion protein comprising the "heterologous polypeptide" and the recited amino acids of SEQ ID NO: 2.

Claims 288-294 are directed to polynucleotides that encode specific epitopes of PDEF disclosed in the specification, and are "operatively associated with" a promoter. There is no support in the original specification for such "operative association". The specification only describes recombinant expression of the epitopes when they are fused to some other polypeptide sequence (pages 25-27). The specification discloses that free epitopes are to be prepared by conventional methods, citing references that describe chemical peptide synthesis, not recombinant protein synthesis (page 24). There is no evidence of record that it was conventional in the art to produce free peptides of this size (9-14 amino acids) by recombinant techniques. Amending claim 288 to include the limitations of claim 264, lines 1-4, (either as a claim dependent from claim 264 or as an independent claim) would overcome this part of the rejection.

Claims 180-182, 184-185, 187-188, 190-191, 193-202, 229, 231, 233-242 are rejected under 35 U.S.C. 112, first paragraph, essentially for the reasons of record set forth in the Office action of 3/16/00 as applied to now cancelled claims 24-26, 28, 29, 31, 32, 34, 35, 37, 38, 40, 41, 43-53, 55, 56, 58, 59, 61, 62, 64, 65, 67-74, 105, 107, 109, 111, and 113-120, because the specification, while being enabling for a "nucleic acid" that encodes SEQ ID NO: 2 or a fragment of SEQ ID NO: 2 (as recited in the claims), does not reasonably provide enablement for polynucleotides that do not encode SEQ ID NO: 2 or a recited fragment of SEQ ID NO: 2. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 180-182, 184-185, 187-188, 190-191, 193-202, 229, 231, 233-242 are drawn to a polynucleotide encoding a polypeptide at least 90% or 95% identical to all or a fragment of SEQ ID NO: 2. (It is presumed that the recited cloned DNA encodes SEQ ID NO: 2.). The claims appear to be directed to polynucleotides that encode proteins or polypeptides, and methods and products for making same, because of recitation of "SEQ ID NO: 2". All of the utilities for polynucleotides taught in the specification require that either the polynucleotide will hybridize with a PDEF nucleic acid or that it encode a polypeptide, either with PDEF function or that can be used to make antibodies that will be specific for a PDEF protein. The specification does not teach any use for a polynucleotide that cannot be used for these purposes.

Any two polynucleotides that encode a given amino acid sequence can be significantly less than 67% identical to each other if all possible wobble bases are different (depending on how many amino acids that have codons with 2 wobble positions are present). This means that sequences encoding the same amino acid sequence could differ by more than every third nucleotide. Relative to a specific polynucleotide, e.g. the open reading frame of SEQ ID NO: 1, the vast majority of polynucleotides that encode the same amino acid sequence would be closer to 65% identical than to 100% identical to the specific polynucleotide; as the sequence identity decreases for the amino acid sequence encoded, the number of polynucleotides increases geometrically. Polynucleotides which differ at every tenth nucleotide, let alone at every third,

will not form stable heteroduplexes (Kennell, Prog. Nucl. Acid Res. Mol. Biol. 11: 259-301, 1971, see para. bridging pages 260-261), and certainly will not at the high stringency conditions required to hybridize to naturally-occurring polynucleotides that encode a given protein such as PDEF. Clearly, even if the claimed invention were limited to nucleic acid sequences encoding SEQ ID NO: 2, the vast majority could not be used in hybridization against any target disclosed in the specification, i.e., SEQ ID NO: 1. The specification does not identify any other target polynucleotides. Further claiming polynucleotides that encode polypeptides that are between 90% to 100% identical to SEQ ID NO: 2 further increases the number of embodiments that are inoperative in hybridization against SEQ ID NO: 1. One skilled in the art would clearly be required to engage in undue experimentation to determine target DNAs for which the inoperative embodiments (relative to SEQ ID NO: 1) could be used.

One skilled in the art might be able to make and use the invention for producing recombinant polypeptides subsequently used for making antibodies against peptides that are part or all of the disclosed PDEF protein or other naturally-occurring human allelic variants of PDEF encoded by DNA encompassed by the claims, which would not be expected to differ substantially from SEQ ID NO: 2. However, the specification does not identify any other naturally occurring PDEF polypeptides, such as homologues from other mammals or allelic variants from humans or any other mammals, whose sequence is within the window encompassed by the claims other than that set forth in SEQ ID NO: 2. In addition to polynucleotides encoding any naturally occurring amino acid sequences that may be embraced by

the claims, the claims also embrace amino acid sequences which do not occur in nature. The specification does not teach that one should make such variants for the purpose of making antibodies against human PDEF (SEQ ID NO: 2); nor is there any evidence of record that one skilled in the art would even consider such a method in the absence of such a disclosure. Such a practice would be seen as counter-productive since it could only reduce the number and specificity of antibodies produced that recognize SEQ ID NO: 2 and increase the number of antibodies that would bind to other polypeptides that are not of interest. As indicated in the specification (page 25, lines 6-9), linear epitopes can be as small as 8-10 amino acids, and identifies (page 25, lines 10-16) only 20 potential small epitopes in PDEF (SEQ ID NO: 2). It is not clear that an antibody that recognizes a peptide sequence differing in 10% or more of amino acids would bind to a PDEF polypeptide or peptide fragment, and not preferentially recognize a peptide sequence derived from another unrelated polypeptide present in a sample. It is unclear how one skilled in the art could predict which of all the possible variant amino acid sequences could be used to make a suitable antibody to the PDEF protein, and the specification provides no guidance on the matter.

The specification does not provide any guidance on what amino acid residues are necessary and sufficient for PDEF biological activity. Neither the specification nor the prior art reveals proteins with any more than cursory amino acid sequence identity to PDEF other than Ets family proteins, which do not share more than general functional properties with PDEF. The specification also provides no teachings on what amino acid sequence modifications, e.g.

insertions, deletions and substitutions, would be permissible in a PDEF polypeptide, that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. It is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976) discloses that even for peptide hormones, which are much smaller than the PDEF protein, that one cannot predict *a priori* variant amino acid sequences for a biologically active polypeptide. Rather one must engage in "case to case painstaking experimental study" to determine active variants (see page 7). Consequently, excessive trial and error experimentation would be required to identify the necessary nucleic acid sequence derivatives encoding a biologically active PDEF protein with an amino acid sequence differing from SEQ ID NO: 2 since the amino acid sequence of such polypeptides could not be predicted.

As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad

> enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st para., if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. This is the case here, where specification discloses only a single amino acid sequence, SEQ ID NO: 2, for a polypeptide having the necessary properties for the disclosed uses, i.e. encoding an active PDEF protein or a polypeptide that could be used to make antibodies against a PDEF polypeptide, and provides no guidance on predicting polypeptide variants of SEQ ID NO: 2 which would be suitable.

Applicant's arguments filed 12/21/01 have been fully considered but they are not persuasive. The fusion proteins of Example 31 contain fragments of SEQ ID NO: 2 which bind to the androgen receptor. No other PDEF biochemical activity was determined. As indicted in the first paragraph of this rejection, polynucleotides that encoded fragments of SEQ ID NO: 2 were deemed enabled. However, the claims embrace far more than N- and C-terminal deletion

fragments of SEQ ID NO: 2 which are at least 90% or 95% of full length SEQ ID NO: 2. The claims also embrace amino acid sequences with substitutions, and internal deletions or insertions.

Allowable Subject Matter

Claims 203-206, 209, 212-228, 243-246, 249, 252-256 and 259 are allowed.

Claims 159-160, 162-163, 165-166, 168-169, 183, 186, 189, 192, 230, and 232 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX numbers are (703) 308-4242 or (703) 305-3014 for any type of communication. In addition, FAX numbers for a computer server system using RightFAX are also available for communications before final rejection, (703) 872-9306, and for communications after final rejection, (703) 872-9307, which will generate a return receipt. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Deborah Clark, can be reached on (703) 305-4051.

Any inquiry concerning administrative, procedural or formal matters relating to this application should be directed to Patent Analyst Patsy Zimmerman whose telephone number is (703) 308-8338. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

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